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EXAMINER
AUDET, MAURY A

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,332	DEVORE ET AL.	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication appears on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *17-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

35 U.S.C. § 112 1st

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain elements is not enabling for others. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for derivatizing collagen with sulfonyl/thiol (SH-) and carboxyl (COO-) "functional groups" (see broad claim 1), does not reasonably provide enablement for derivatizing collagen with a "functional group" from any and all species of what constitutes the genus "a functional group" (claim 1). The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specification page 9 (and generally throughout the specification) reasonably describes that "[d]erivatization was intended to provide functional groups to enhance both cohesive (SH-, thiol) and adhesive (COO-) characteristics", and that these specific "functional groups" were selected for their respective derivatizing qualities (i.e. SH- for cohesive strength; COO- for adhesive strength). However, the specification does not describe that any other functional groups could replace the two described "functional groups" (SH-; COO-) and produce a derivatized collagen capable of the cohesive and adhesive strength necessary to make the invention work. Applicant has not enabled such a broad scope.

Ellis et al. (1999) list 41 organic functional groups (Table 1), which are capable of reacting with proteins such as collagen, under the right conditions. As broadly claimed, the present invention as claimed, encompasses any one of Ellis et al.'s 41 organic functional groups. However, it is unpredictable whether even one of these could replace the "functional groups" described in the present specification. Furthermore, as Wallace et al. teach at column 31, lines 1-9, it took more than 100 hours of hydration in the study of simulated in vivo analysis of derivatized collagen to postulate that "weakening of bond strength was *thought* to be due to hydrolysis of carboxyl -ester and thio-ester (FIG. 13) network linkages. COH102 is a glutaryl-succinimidyl ester; even after reaction with the terminal carboxyl of the succinimidyl ester, there remains a carboxyl ester linking the glutaryl moiety to the main PEG chain; this bond, as well as the thio-ester bond, could hydrolyze" (emphasis added in original). Assuming it may only be possible to determine "functional group" bond strength by similar tests, the amount of time and

effort to determine whether other "functional groups" could work in the invention would involve undue experimentation. Thus, determining whether any and all functional groups could elicit tissue cohesion and adhesion qualities, the two qualities described in the specification as essential to the invention's functionality, would require undue experimentation without a reasonable expectation of success by one of skill in the art.

Applicant may overcome the rejection by amending claim 1 to incorporate "said derivatized collagen consisting of SH- and COO- functional groups" (i.e. dependent claims 2 and 3 and the "functional groups" described by the specification).

Along similar lines as subsection a. above, claims 1-16 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition with 'both' COO- and SH- functional groups (plural), is not necessarily enabled for a composition with only 'a' functional group (singular; either COO- or SH-). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specification page 9, 1st paragraph, describes that "[d]erivatization was intended to provide functional groups [plural] to enhance both cohesive and adhesive characteristics"; expressly describing throughout that SH- (thiol) is needed for cohesive strength, and COO- (carboxyl) for adhesive strength. Thus, the description has expressly described that the invention (composition) must have both SH- and COO- functional groups (plural); otherwise either cohesive or adhesive strength is absent or insufficient.

As discussed above, Wallace et al. teach, at column 31, lines 1-9, that it took more than 100 hours of hydration in the study of simulated *in vivo* analysis of derivatized collagen to postulate that certain bonds may be weakened more readily than others. Likewise, it could take even more hours to test whether a composition with collagen derivatized with only COO- (adhesive) or only SH- (cohesive), will be capable of functioning as an adhesive/sealant in certain procedures but not others (due to the lack of cohesive/adhesive strength needed). Applicants have not enabled such a broad scope of a composition working as an adhesive with only COO- or only SH- derivatized to the collagen.

Applicant may overcome the rejection by amending claim 1 to incorporate "said derivatized collagen consisting of SH- and COO- functional groups" (i.e. dependent claims 2 and 3 and the "functional groups" described by the specification).

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a "concentration" [of derivatized collagen] ranging from 300 mg/ml (30%) to 800 mg/ml, does not reasonably provide enablement for a "at least equal to 300 mg/ml" (claim 1) without the addition of "800 mg/ml" as the upper limit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specification page 3, ¶ 2, reasonably describes that the "compositions are comprised of chemically derivatized soluble collagen, which is formulated to *concentrations* ranging from 300 mg/ml (30%) to 800 mg/ml (80%) collagen protein" (emphasis added in original). Further, on the middle of page 10, the specification describes that "[l]yophilized derivatized collagens were

formulated into viscous compositions having from 30-80% collagen solids. Since collagen typically becomes saturated at less than 10% solids, *novel techniques were developed* to increase total collagen concentrations to 30-80%" (emphasis added in original). Based on the specification description, it can only be assumed that derivatized collagens containing "less than 10% solids" were being used in the art at the time of the invention, and that Applicant specifically found a novel technique to raise this percentage and that the percentage 300mg/ml (30%) to 800 mg/ml (80%) was found to be essential to the invention's functionality. Were this not the case, the only reasonable assumption is the specification would have described a functional concentration of any percentage around 100 mg/ml (10%) (i.e. just above the known solid concentration) to 800 mg/ml (80%) collagen solids. Applicants have not enabled such a broad scope of any "concentration".

As discussed above, Wallace et al. teach, at column 31, lines 1-9, that it took more than 100 hours of hydration in the study of simulated *in vivo* analysis of derivatized collagen to postulate that certain bonds may be weakened more readily than others. Likewise, it could take even more hours to test the specific collagen percentages necessary to work properly as a "tissue adhesive". As broadly claimed, it is necessarily unpredictable as to whether any amount other than 30-80% would allow adequate long-term tissue adhesion in the present invention. Thus, determining whether a collagen solid concentration above or below 300 mg/ml (30%) to 800 mg/ml (80%) could elicit the necessary tissue cohesion and adhesion qualities, would require undue experimentation without a reasonable expectation of success by one of skill in the art.

Applicant may overcome the rejection by amending claim 1 to incorporate the following or similar recitation: "at least equal to 300 mg/ml (30%) up to 800 mg/ml (80%);" (i.e. the latter range of claim 4 and the "concentration" described in the specification).

Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition with "biodegradable"/biocompatible materials (i.e. derivatized collagen, antibacterial agent, water, collagen fibrils/fibers/fiber bundles) for use as a tissue adhesive on living animals/mammals, does not reasonably provide enablement, under present medical studies, for the addition of cyanoacrylate (or species thereof) to such a composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specification page 12, 3rd ¶ recites that "a layer of cyanoacrylate . . . can be initially applied to tissues [] [t]he cyanoacrylate layer is believed to interact with NH2 groups in protein molecules in tissues [] to initiate nucleophiles, kicking-off monomer polymerization and bonding to protein surfaces. In particular, derivatized collagen formulations [] were combined with . . . cyanoacrylates." The specification does not discuss the biocompatibility or potential harmful affects of cyanoacrylates on tissues.

The state of the art indicates at least four references that teach cyanoacrylates are contraindicated for use as tissue adhesives due to biocompatibility issues and toxicities associated with tissue sealing. Kelman et al. teach:

> Attempts to provide desired adhesion through mechanical bonding have proven to be neither convenient nor permanent. [] For this reason, much attention was devoted to

> developing synthetic polymers, e.g., cyanoacrylates, as biomedical adhesives. These plastic materials, however, have been observed to induce inflammatory tissue reaction. Moreover, the ability of these materials to establish permanent bonding under physiological conditions has yet to be fully realized. [column 1, lines 10-20]

Wallace et al. teach that via reference that "Polymerizable cyanoacrylates have also been described for use as tissue adhesives (Ellis, et al., J. Otolaryngol. 19:68-72 (1990))" (column 1, lines 49-51). Wallace et al. further teach that:

> Cyanoacrylate is a highly effective adhesive that forms a strong matrix, but is *too toxic to be used internally* and is thus not approved for such uses. Accordingly, it is an object of the present invention to provide compositions that form high strength medical sealants that are not toxic. [Column 2, lines 7-12]

Wallace et al. specifically teach that internal use of cyanoacrylates is toxic, but necessarily leaves in question, like Kelman et al., whether cyanoacrylates should be used externally either. Thus, the objective of the Wallace et al. invention in fact was to design a composition comprising derivatized collagen for tissue adhesion, as an alternative to toxic and non-biocompatable (i.e. inflammation and fibrosis causing) cyanoacrylates (i.e. SUPERGLUE™, KRAZY GLUE™), yet with the strength of cyanoacrylates (columns 3 and 4).

Nielson et al. teach:

> The adhesive properties of certain cyanoacrylate esters was discovered by Coover in 1959 (H. W. Coover, et al. (1959) J. Soc. Plast. Eng. 15:5). Over the past two decades cyanoacrylates, in particular *n-butyl cyanoacrylate* and iso-butyl cyanoacrylate, have been widely used in surgery as tissue adhesives and as wound coverings (M. L. Ronis, et al. (1984) Laryngoscope 94:210-213; S. Sabanathan (1993) Eur. J Cardiothorac. Surg. 7:657-660; A. B. Leahey, et al. (1993) Ophthalmology 100:173-180). N-butyl cyanoacrylate has been used in more than one thousand eye surgeries and larynx repairs (see, for example, A. B. Leahey, et al. (1993) Ophthalmology 100:173-180, and references cited therein). Various formulations of cyanoacrylate (as the Nexaband.RTM. family of products, Tri-Point Medical, Raleigh, N.C.) are widely used in veterinary medicine as wound dressings.

Nielson et al. further teach the use of "n-octyl" and "n-butyl" cyanoacrylates (claim 25) [Applicant's claims 12-13] as applied to epithelial collagenous tissue for hair growth, but do not discuss the potential side effects.

Reece et al. (2001, Amer. J. of Surg.) teach that cyanoacrylates are "not bioabsorbable [i.e. biodegradable, one of Applicant's claim limitations]; the body cannot break them down"; "[i]f not used topically, cyanoacrylates are foreign bodies that could induce internal inflammation, tissue necrosis, and infection risks associated with foreign bodies (p. 41S, column 2, last 2 ¶'s). Reece et al. finally indicate that "as a class cyanoacrylates have many uses, but they are restricted to external or temporary applications" (page 42S, column 1, last s.).

Based on Nielson et al. and Reece et al. it appears cyanoacrylates are capable of non-bioabsorbable exterior use; however, Kelman et al., Wallace et al. and Reece et al. strongly contraindicate any internal use of cyanoacrylates. Thus, not only is it unpredictable as to whether cyanoacrylates may be used in ANY internal use, such use is entirely contraindicated. Determining whether the use of cyanoacrylates alone or in combination with the derivatized collagen composition would not toxic, inflammation-inducing, or carcinogenic in any form of internal use would require undue experimentation without a reasonable expectation of success by one of skill in the art.

Based on the state of the art and the limited description of use of cyanoacrylates in the specification, it is suggested that the claims be amended in one of the following ways:

i) to only recite the use of cyanoacrylates (and n-butyl/n-octyl) for external tissue adhesing only and remove the limitation of claim 8 wherein the composition is "biodegradeable"; or

ii) remove the limitations drawn to cyanoacrylates; or

iii) create two independent claims drawn to separate natures of the inventions, as can be understood by i) and ii) above.

If i) is done, (see § 112 2nd rejection above) Applicant would no longer have a bioabsorbable [biodegradable] composition; therefore, the invention could not equally have limitations drawn to a biodegradeable and cyanoacrylate-added composition.

In response to the 112 1st scope of enablement rejections, Applicant is asked to claim in full, clear, concise and exact terms, the elements of the invention as to enable *any* person skilled in the art to make and use the invention as claimed.

35 U.S.C.§ 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to "a composition comprising": " a derivatized collagen" and then "a concentration of said derivatized collagen". It is unclear whether Applicant is claiming a composition with derivatized collagen (an entire amount) or merely a concentration of derivatized collagen?

The rejection may be overcome by amending the claim using "product by process" language, or removing "a derivatized collagen" and "said" and leading line two with "a concentration of [] derivatized collagen . . .".

Claim 1 is drawn to a derivatized collagen having a "functional group". It is unclear what is contemplated within the meaning of "functional group" (see also § 112 1st rejection above). The structure of a typical collagen molecule contains a triple helix, generally yielding more than a total of 3,000 amino acids, wherein all but glycine may have functional groups attached (See Alberts et al., Fig.19-40, p. 979). Since glycine is prevalent in the collagen molecule, it is indefinite as to where the functional groups of the derivatized collagen are capable of being attached? Claims 2 and 3 recite specific functional groups; however, no indication of what amino acids they are to be attached, is indicated. It was not found in the specification where the functional groups in question were to be attached within the collagen molecule.

The rejection may be overcome by Applicant pointing out where in the specification such information is provided, or with evidence that it was well known in the art at the time of filing where a "functional group" is to be attached/derivatized (specific amino acid) of the collagen protein, to create the invention's cohesive and adhesive strength.

Claim1 is drawn to derivatization with a "functional group" (singular), and claims 2 and 3 separately claim that COO- or SH- may be the "functional group". However, specification page 9, 1st paragraph, describes that "[d]erivatization was intended to provide functional groups [PLURAL] to enhance both cohesive and adhesive characteristics"; expressly describing throughout that SH- (thiol) is needed for cohesive strength, and COO- (carboxyl) for adhesive strength. Thus, it is unclear what the invention is; a composition with both cohesive and adhesive strength or a composition with only cohesive or adhesive strength; since the claims leave this seemingly essential characteristic unclear.

The rejection may be overcome by amending claim 1 to incorporate "said derivatized collagen consisting of SH- and COO- functional groups" (i.e. dependent claims 2 and 3 and the "functional groups" described by the specification).

Claim 5 recites the limitation "said liquid, gel or solid". There is insufficient antecedent basis for this limitation. The rejection may be overcome by removing "said liquid, gel, or solid" and replacing with "said concentration".

Claim 8 is drawn to a "biodegradable" composition and claim 11-13 are drawn to the addition of cyanoacrylate (n-butyl and n-octyl) to the composition. However, Reece et al. (2001, Amer. J. of Surg.) teach that cyanoacrylate is not bioabsorbable [biodegradable] (column 41S, column 2, 2nd to last ¶). Thus, if cyanoacrylate is added to the composition, it is no longer biodegradable. Since Applicant's claim set is drawn to a single independent claim, if is unclear how the invention can be both biodegradable and cyanoacrylate-containing.

The rejection may be overcome by amending the claims according to § 112 1st rejection c., above.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 1, 4-9, and 14-16 are rejected under § 102 (e), as anticipated by Wallace et al. (US 6495127 B).

Wallace et al. teach a composition gel (column 12, line 37); solid (i.e. hardened gel, column 27, line 19); liquid (i.e. soluble collagen derivatives or pre-gel phase; column 13, lines 47-48) comprising a derivatized collagen (column 12, lines 56-57) being at least equal to 300 mg or 400 mg to 800 mg (column 27, lines 10) and having a functional group (claim 21) being a pH in a range of 6.8 to 7.8 (column 13, lines 47-48); and being biodegradable (column 9, lines 66-67 and column 10, lines 1-2; and inherent quality of collagen, a tissue substance). The composition may further comprise an antibacterial agent (claim 25); water (column 12, lines 45-51); material selected from the group of collagen fibrils, fibers, or fiber bundles (i.e. "afibrillar, microfibrillar [i.e. fibrils] or fibrillar [i.e. fibers] collagen" (column 10, lines 45-46, and claims 14-17)) of at least equal to 50 mg/ml (column 21, lines 61-67).

Therefore, the reference is deemed to anticipate the instant claims above.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-10, and 14-16 are rejected under § 102 (e), as anticipated by Wallace et al. (US 6495127 B).

Kelman et al. teach a collagen composition with at least one of an acylating agent (glutaric anhydride, claim 7) and sulfonating agent (claim 17) to derivatize collagen thus yielding COO- and SH- functional groups, respectively [which could intrinsically yield 300-800 mg if derivatized to said degree]; at a pH in a range is 6.8-7.8 (column 5, lines 1, 6, 28-30 and 38-40); biodegradeable (column1, lines 41-46); comprising an antibacterial agent (column 6, lines 64-68, and column 7, lines 1-2); in water (column 9, line 33); and as a gel, solid, and liquid (intrinsically, with the different phases of the composition from formation to application to tissue sealant).

Therefore, the reference is deemed to anticipate the instant claims above.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. in view of Kelman et al. (US 5129895) and Devore et al. (6161544).

The claimed invention is discussed above.

Wallace et al is described above. Wallace et al. teach derivatizing collagen with methyl, ethyl, propyl, or benzyl groups (claim 21) and teach that "other derivatives of collagen which remain soluble [] at pH 4-7, can also impart the same desired properties." However, Wallace et

al. does not specifically teach derivatizing with COO- and SH- functional groups. [Applicant's claims 2-3].

Kelman et al. is discussed above. Kelman et al. teach the use of "at least one of an acylating agent (glutaric anhydride, claim 7) and sulfonating agent" (claim 17) to derivatize collagen thus yielding COO- and SH- functional groups.

Devore et al. does specifically teach the use of 4-Mercapto-1,8,Napthalic Anhydride (as Applicant used), to yield the SH- functional group.

Both Kelman et al. and Devore et al. teach many sulfonating agents, as suitable, but non-limiting examples; all capable of carrying out the same function of derivatizing with an SH-functional group.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to derivatize the collagen of Wallace et al. to form "other derivatives of collagen" with the glutaric anhydride of Kelman et al. to yield the COO- functional group, and either the sulfonating agents of Kelman et al. or the 4-Mercapto-1,8,Naphthalic Anhydride of Devore et al. [column 6, line 49], because it was known that COO- provides adhesive strength and SH- provides cohesive strength, desired properties of a collagen-based tissue adhesive.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. in view of Caroli et al. (1997, Ann Chir Main Memb Super) and further in view of Nielson et al. (US 5767152).

Wallace et al. teach a tissue adhesive for external or internal use, but specifically teach away from the use of cyanoacrylates with derivatized collagen because the use of cyanoacrylates (toxic) would render the composition toxic for *internal* use as tissue adhesives (column 2, lines 7-13). [Applicant's claims 11-13] However, Wallace et al. does not teach that the use of cyanoacrylates would be toxic in a composition for external tissue adhesive use; teach that cyanoacrylates "are highly effective adhesive[s] that forms a strong matrix" (column 2, lines 7-8; column 1, lines 49-50); and use cyanoacrylate [SUPERGLUE] as the model adhesive by which to carry out comparison tests of the present invention against (column 28, lines 36-39).

Caroli et al. teach the use of a cyanoacrylate as a biological tissue adhesive in a composition *with* collagen, the former having high adhesive properties and the latter having biocompatible ("biological") properties (abstract).

Nielson et al. is fully discussed under § 112 1st subsection c., above, regarding the use of cyanoacrylates as tissue adhesives, and n-octyl and n-butyl forms. Nielson et al. necessarily teach that cyanoacrylates (including n-octyl and n-butyl (claim 25)) may be used *at least externally*. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the cyanoacrylates (specifically n-butyl and n-octyl) of Nielson et al. in the tissue adhesive composition comprising derivatized collagen of Wallace et al. for *external* tissue adhesive use, because Caroli et al. teach the use of cyanoacrylates with collagen in an adhesive, Nielson et al. teach the external use of the specific cyanoacrylates n-butyl and n-octyl,

and Wallace et al. teach the favorable strength of cyanoacrylates and does not teach against its used in external applications. along with teaching a history of cyanoacrylates as the desired tissue adhesive in thousands of external surgeries.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
May 9, 2003

CHRISTOPHER R. TATE
PRIMARY EXAMINER